solution was filtered and concentrated under reduced pressure to give the crude product as a brown oil (13.3 g, 80%), spectroscopically almost indistinguishable from pure material. Simple distillation under reduced pressure afforded pure material, a pale yellow oil: 10.8 g; 65%; bp 108–110 °C (0.5 torr); freezes at ca. 15 °C; n^{27}_D 1.5325; IR (liquid) 3050, 2950, 1750, 1680, 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (s, 3 H, $CH_3C{=}O$), 3.2 (s, 3 H, CH_3N), 7.1 (s, 5 H, C_6H_5). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.80; H, 6.32%.

b. Pyruvyl chloride (1.1 g) was added dropwise to a solution of *N*-methylaniline (0.75 g) and pyridine (1.1 g) in $CHCl_3$ (5 mL). The solution was washed with water and concentrated under reduced pressure to give essentially pure product (1.25 g) in practically quantitative yield. Distillation (0.5 torr) afforded almost colorless material, 1.0 g, 80%.

c. Finely powdered *N,N'*-dimethyloxanilide (26 g) was added portionwise to a stirred solution of methylmagnesium iodide (from Mg, 10.5 g, and CH_3I, 53 g) in ether (500 mL). The mixture was stirred for 3 h, ice and 6 M HCl (160 mL) then were added, the ether layer was isolated, dried ($MgSO_4$), and evaporated, and the crude product was obtained as a red-brown oil (11.2 g), the spectroscopic properties of which were consistent with a 1:1 mixture of *N*-methylpyruvanilide and unreacted dimethyloxanilide. Simple distillation did not effect separation but fractionation by means of a Nester-Faust annular adiabatic spinning band column afforded 4.4 g, 26%, of reasonably pure material.

1,3-Dimethyl-3-hydroxyoxindole. *N*-Methylpyruvanilide (1 g) was placed on a large watch glass, covered with concentrated HCl (2–3 mL), and heated on the steam bath until the aqueous acid was evaporated away (20–30 min). Occasionally, the product obtained upon cooling being oily or pasty, the acid treatment would be repeated. Crystallization of the solid product from water afforded the oxindole as snowy crystals: 0.55 g; 55%; mp 152–3 °C; spectroscopic and analytical properties were in complete agreement with published data.[8]

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Registry No.—*N*-Methylpyruvanilide, 61110-50-7; pyridinium hydroxymaleic anhydride, 52060-80-7; *N*-methylaniline, 100-61-8; pyruvyl chloride, 5704-66-5; *N,N'*-dimethyloxanilide, 14288-22-3; methylmagnesium iodide, 917-64-6; 1,3-dimethyl-3-hydroxyoxindole, 54279-13-9.

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Revision of Some 16-Alkylated Steroids

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The introduction of a 16-methyl substituent into the steroid nucleus is a common procedure to enhance biological activity in the corticoid series. This effect, however, is not observed with the other classes of steroidal hormones, such as androstanes, estranes, and aldosterone antagonists, which upon 16-alkyl substitution show a marked decrease in hormonal activity. These less active classes of compounds, however, have become of new interest since some 16-ethylestranes have recently been shown to exhibit antihormonal activity.[1]

Our first aim was to find a stereoselective introduction of 16α-alkyl substituents starting from 17-ketosteroids, for we believe that the apparent lack of methods in this respect is largely responsible for certain shortcomings and errors in the literature.

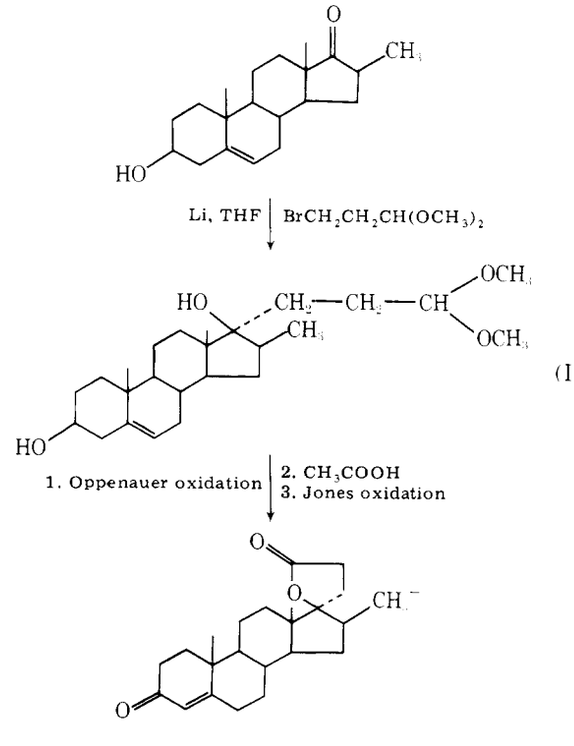
The problem was solved by adopting the procedure of Corey and Enders.[2] Alkylation of 17-ketodimethylhydrazones resulted in clean and quantitative formation of the 16α-alkyl derivatives. Hydrazone cleavage with cuprous chloride in aqueous tetrahydrofuran led to regeneration of the parent ketone without isomerization at C-16.[3,4]

The application of the Corey–Enders procedure to a rigid five-membered ring ketone demonstrates that, in this case, stereoselectivity can only be explained on the basis of steric factors, as orbital control would not be expected to distinguish between α or β side attack.[10]

The stereoselective synthesis of 16β-methyl steroids was performed according to known methods.[5] With pure 16α- and 16β-methyl isomers at hand[6] we investigated the question of thermodynamic stability which had been a point of controversy between several research groups.[7–9] Treatment of 3β-hydroxy-16β-methyl-5-androsten-17-one as well as 3β-hydroxy-16α-methyl-5-androsten-17-one under acidic or alkaline conditions led to the same equilibrium mixture which contained the 16β-methyl derivative in about 80% and the 16α-methyl isomer in about 20%. This is not in agreement with Atwater's[7] result who claimed complete conversion of the β isomer into the α compound.

A comparison between our material and Atwater's[7] revealed significant differences as far as the 16α-methyl compound is concerned.

The steric hindrance exercised by a 16α or β substituent is another point of discussion. Atwater et al.[7] reported that their repeated attempts to ethynylate 3β-hydroxy-16β-methyl-5-androsten-17-one were unsuccessful. Our results show,



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however, that a kinetically controlled ethynylation[11] of that compound proceeds quite cleanly with formation of a single isomer resulting from α side attack.

Ethynylation of the 16α isomer also occurs predominantly from the α side although in this case the isomeric ethynyl alcohol is formed to a minor extent, too.

As these results were not in agreement with those reported by Atwater et al.[7] we reinvestigated their synthesis of 16α-methylspironolactone. The sequence of reactions in eq I was applied to both 3β-hydroxy-16β-methyl-5-androsten-17-one and its 16α isomer.[12]

In the 16β-methyl case we obtained a single lactone the physical and spectroscopic data of which were in agreement with the compound to which Atwater et al.[7] wrongly ascribed the 16α-methyl configuration.

The 16α-methyl compound was converted into a mixture of lactones which were separated by chromatography and identified as 16α-methyl compounds isomeric with respect to position C-17.

Experimental Section

3β-Hydroxy-16β-methyl-5-androsten-17-one:[5] mp 165–168 °C; $[\alpha]_D$ +4° ($CHCl_3$, *c* 0.5); ^1H NMR δ 0.84 (s, 3 H, H-18), 1.03 (s, 3 H, H-19), 1.22 (d, J = 7 Hz, 3 H, 16β-CH_3), 3.50 (m, 1 H, H-3), 5.38 (m, 1 H, H-6); IR (KBr) 3480 cm^{-1}, 1733; CD (dioxane) λ 301 nm ($\Delta\epsilon$ = +2.84), 307 (+3.31), 317 (+2.44).

3β-Hydroxy-16α-methyl-5-androsten-17-one. 3β-Hydroxy-5-androsten-17-one was protected as its 3-THP ether. Hydrazone formation, alkylation (using 2.2 equiv of *n*-butyllithium at 0 °C, 60 min), and hydrazone cleavage were performed following the literature scheme.[2,3] Hydrazone cleavage is accompanied by THP ether hydrolysis, if the reaction time is prolonged to 15 h: mp 145–148 °C; $[\alpha]_D$ −13° ($CHCl_3$, *c* 0.505); ^1H NMR ($CDCl_3$) δ 0.94 ppm (s, 3 H, H-18), 1.05 (s, 3 H, H-19), 1.10 (d, J = 7 Hz, 3 H, 16α-CH_3), 3.50 (m, 1 H, H-3), 5.39 (m, 1 H, H-6); IR (KBr) 3490 cm^{-1}, 1728; CD (dioxane) λ 304 nm ($\Delta\epsilon$ = +2.84).

Equilibration. 3β-Hydroxy(acetoxy)-16α-methyl-5-androsten-17-one as well as its 16β isomer were subjected to the equilibrating conditions of Bowers et al.,[8] the reaction times being prolonged to 24 h. Composition of the equilibrium mixture (by NMR): 78.5% of β-methyl, 21.5% of α-methyl.

Ethynylation. The ethynylations were performed according to the procedure of Phillips et al.[11]

17α-Ethynyl-16β-methyl-5-androstene-3β,17β-diol: mp 209–212 °C; $[\alpha]_D$ −97.6° ($CHCl_3$, *c* 0.505); ^1H NMR δ 0.84 (s, 3 H, H-18), 1.04 (s, 3 H, H-19), 1.10 (d, J = 7 Hz, 3 H, 16β-CH_3), 2.56 (s, 1 H, C≡CH), 3.50 (m, 1 H, H-3), 5.33 (m, 1 H, H-6); yield[13] 92%.

17α-Ethynyl-16α-methyl-5-androstene-3β,17β-diol: mp 221–223 °C; $[\alpha]_D$ −129.7° ($CHCl_3$, *c* 0.505); ^1H NMR δ 0.92 ppm (s, 3 H, H-18), 1.03 (s, 3 H, H-19), 1.16 (d, J = 7 Hz, 3 H, 16α-CH_3), 2.60 (s, 1 H, C≡CH), 3.51 (m, 1 H, H-3), 5.35 (m, 1 H, H-6); yield[13] 72%.

Lactones. The sequence of Radscheit et al.[12] (addition of 3-lithiopropionaldehyde dimethyl acetal, Oppenauer oxidation, acetal hydrolysis, Jones oxidation) was employed in the synthesis of the following lactones:

3-(3-Oxo-16β-methyl-17β-hydroxy-4-androsten-17α-yl)propionic acid lactone: mp 176–177 °C; $[\alpha]_D$ + 95.4° ($CHCl_3$, *c* 0.500); ^1H NMR ($CDCl_3$) δ 0.96 (s, 3 H, H-18), 1.06 (d, J = 7 Hz, 3 H, 16β-CH_3), 1.20 (s, 3 H, H-19), 5.74 (m, 1 H, H-4); IR (KBr) 1768 cm^{-1}, 1670, 1610; yield[13] 68%.

3-(3-Oxo-16α-methyl-17β-hydroxy-4-androsten-17α-yl)propionic acid lactone: mp 180–182 °C; $[\alpha]_D$ +49.5° ($CHCl_3$, *c* 0.505); ^1H NMR ($CDCl_3$) δ 1.00 ppm (d, J = 7 Hz, 3 H, 16α-CH_3), 1.04 (s, 3 H, H-18), 1.20 (s, 3 H, H-19), 5.73 (m, 1 H, H-4); IR (KBr) 1770, 1672, 1612 cm^{-1}; yield[13] 32%.

3-(3-Oxo-16α-methyl-17α-hydroxy-4-androsten-17β-yl)propionic acid lactone: mp 218–220 °C; $[\alpha]_D$ +51.4° ($CHCl_3$, *c* 0.505); ^1H NMR ($CDCl_3$) δ 0.86 (s, 3 H, H-18), 1.01 (d, J = 7 Hz, 3 H, 16α-CH_3), 1.19 (s, 3 H, H-19), 5.74 (m, 1 H, H-4); IR (KBr) 1760, 1675, 1612 cm^{-1}; yield[13] 34%.

Registry No.—3β-Hydroxy-16β-methyl-5-androsten-17-one, 67843-75-8; 3β-hydroxy-16α-methyl-5-androsten-17-one, 2891-00-1; 3β-acetoxy-16β-methyl-5-androsten-17-one, 2099-24-3; 3β-acetoxy-16α-methyl-5-androsten-17-one, 2099-25-4; 17α-ethynyl-16β-methyl-5-androstene-3β,17β-diol, 67800-69-5; 17α-ethynyl-16α-methyl-5-androstene-3β,17β-diol, 67800-70-8; 3-(3-oxo-16β-methyl-17β-hydroxy-4-androsten-17α-yl)propionic acid lactone, 67827-36-5; 3-(3-oxo-16α-methyl-17β-hydroxy-4-androsten-17α-yl)propionic acid lactone, 67800-71-9; 3-(3-oxo-16α-methyl-17α-hydroxy-4-androsten-17β-yl)propionic acid lactone, 67843-76-9.

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(13) Yields refer to 3β-hydroxy-16β-methyl-5-androsten-17-one or to its 16α isomer.
(14) Satisfactory analytical data were obtained for all compounds mentioned in the Experimental Section.

Synthesis of (±)-Norisoambreinolide and (±)-Isoambrox[1]

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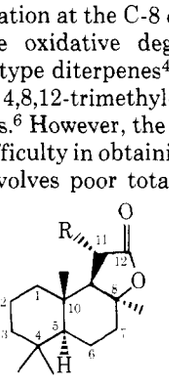
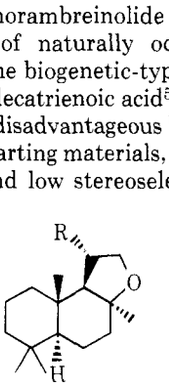
Norisoambreinolide (**1a**)[2] and isoambrox (**2a**),[3] amberlike odorous compounds, have been the object of numerous synthetic studies.[4-7] The major approaches to **1a** consist of (a) epimerization at the C-8 carbon of norambreinolide derived from the oxidative degradation of naturally occurring labdane-type diterpenes[4] and (b) the biogenetic-type cyclization of 4,8,12-trimethyl-3,7,11-tridecatrienoic acid[5] and its analogues.[6] However, the former is disadvantageous because of the difficulty in obtaining pure starting materials, and the latter involves poor total yields and low stereoselectivity.



1a, R = H
b, R = SO_2Ph



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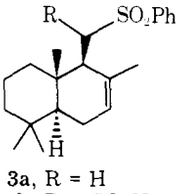
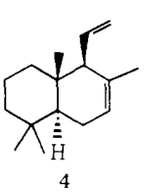


3a, R = H
b, R = CO_2H
c, R = CH_2OH



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